UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/173,864	10/16/98	IVARIE R	24011-0002

HM22/0808
HELLER EHRMAN WHITE & MCAULIFFE
525 UNIVERSITY AVENUE
PALO ALTO CA 94301-1900

EXAMINER	
KAUSHAL,S	
ART UNIT	**PAPER NUMBER**
1633	12

DATE MAILED: 08/08/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/173,864	IVARIE et al
Examiner	**Group Art Unit**
SUMESH KAUSHAL	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *19, 21, 25, 27, 29, 33-35, and 41-57* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *19, 21, 25, 27, 29, 33-35, and 41-57* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachm nt(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. Claims 19, 21, 25, 27, 29, 33-35, 41-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or use the invention**.

The instant claims are drawn to transgenic birds wherein the exogenous transgene is expressed in the tubular gland cells of the avian oviduct wherein the constitutive promoter is CMV promoter. The claims are also drawn to a method of producing an avian egg from a transgenic avian which contains an exogenous protein, wherein the protein is secreted into the oviduct lumen so that the protein is deposited in the yolk of an egg. The claim is also drawn to a method of producing an egg wherein the vector used to make the transgenic avian encodes two coding sequences wherein the second coding sequence is capable of providing post translational modification of the protein encoded by the first coding sequence, wherein an internal ribosome entry site element (IRES) is positioned between first and second coding sequence. The claims are also drawn to a method of producing an exogenous protein in an avian oviduct by making a transgenic avian, wherein the protein is expressed in tubular gland cells of transgenic avian. The claims are also drawn to a transgenic bird having a transgene in the genetic material of the tubular gland cells of its magnum, and the transgene is expressed in the tubular gland cells of the transgenic bird. The claims are also draw to a transgenic bird expressing an exogenous gene in the tubular gland cells of its magnums, wherein the protein is

deposited in onto the yolk of an egg of that bird. In addition, claims are drawn to a transgenic avian and eggs thereof wherein the transgene is interferon.

The specification teaches making of an ALV-base retroviral vector wherein the CMV promoter derives the expression of b-lactamase (example-1 and 2). The specification teaches production of chimeric chickens transducing stage X embryos with NLB-CMV-BL retroviral particles (page 34, line 10-15). The specification further teaches the detection of b-lactamase activity in the egg white of chimeric chickens (page 36 table-1). The transgenic animals are the animals where an exogenous transgene is integrated into the DNA of germ cells and the animals are capable of transmitting the transgene to their progeny. However, the specification fails to show even a single transgenic founder obtained from chimeric chickens, capable of producing a transgenic progeny expressing the b-lactamase activity in oviduct and/or eggs in any and all offsprings. Therefore, it is not clear how one skilled in the art would use the invention as claimed without excessive and undue amount of experimentation required in the making of transgenic birds.

The art at the time of filing teaches that the making of transgenic birds is highly unpredictable because the complexities of egg formation make the earliest stages of chick-embryo development relatively in-accessible (Sang TIBTECH 12:415-420, 1994, page 415, col.2 para.2). Furthermore, the making of chimeric birds is technically demanding as its requires the development of methods that enhances the survival of embryonic cells and an increase in frequency of chromosomal integration of injected DNA (Sang, page 416, col.1 para.3). Furthermore, ex-vivo transfection of blastodermal cells and reimplantation into an egg has not show to transmit the transgene through germ lines. In addition, the development of chicken embryonic stem cells that can be grown for longer periods in culture to allow the targeted recombination events is highly unpredictable (Sang page 417, col.1 para. 1-2). Therefore, considering the unpredictable nature of avian transgenic art, the specification as filed

fails to disclose a single working example of any transgenic bird that would enable one skill in the art use the invention as claimed without excessive and undue amount of experimentation.

Furthermore, replication defective retroviral vector has been used to obtain germ line transmission of transgenes resulting in a wide variety of tissues, however tissue-specific expression has not been achieved (Simkiss, Transgenic birds, animals with novel genes, Mclean ed, Cambridge Univ.Press NY pages 106-137, 1994, see paragraph bridging pages 118-119). The specification fails to show the expression of any exogenous protein in the tubular gland cells of oviduct or magnum tissue of any and all birds. The specification provided a prophetic example in fig-6 which illustrates magnum-specific gene expression in magnum and non-magnum cells (page 13, line 9-13). The specification only teaches the detection of b-lactamase in egg white obtained from a chimeric chicken (page 36, table-1) which is not representative of any transgenic bird.

The art at the time of filing teaches that yolk proteins are synthesized by liver and accumulates in the yolk by a receptor mediated process few days before ovulation. Sang teaches that the yolk proteins require specific internal recognition sequences for uptake into yolk and it is easier to modify protein genes to direct incorporation of foreign proteins into egg white (Sang, page 418, col.2, para. 3). The specification as filed fails to disclose any signal sequences that direct the deposition of a protein to egg yolk. Thus, considering the state of the art and the guidance provided in the specification one skill in the art would be unable to use the invention as claimed without excessive and undue amount of experimentation.

In addition, the method of providing post-translational modification of the proteins deposited in an avian egg is not enabled because specification fails to disclose the enzyme required for the post-translational modification of any proteins deposited into an egg. The specification fails to teach the claimed genetic construct encoding a protein, an IRES element and a second encoding sequence

required for post-translational modification of the protein of interest. The specification only exemplified that the first coding sequence may encode collagen which would be hydroxylated and made active by an enzyme encoded by the second coding sequence. The specification fails to disclose a single working example wherein any post-translational modified protein is deposited in an egg (see page 23 lin 23, App. Spec). The state of the art at the time of filing was such that various factor affects the extent of the post translational modification of proteins. For example, besides the type of enzyme used for the post translational modification of collagen, one of the critical factor that regulates the collagen post-translational modification is the ratio of enzyme to substrate in the cell. (Myllya et al, Biochem. J. 196:683-692, 1981, see page 691, col.2 lin.1). The specification fails to disclose a specific modulating enzyme for post translational modification of collagen or any other protein of interest and fails to show the claimed post translational modification of any protein. In addition, the specification fails to show the deposition of any and all exogenous protein in an avian egg, which is post translationally modified using the claimed di-cistronic vector, encoding any and all proteins and modifying enzymes.

Thus, in view of lack of specific guidance in the specification and considering the state of the art, the skilled artesian at the time of filing would be unable to use the claimed invention, without an excessive and undue amount of experimentation. The quantity of experimentation required would include making any and all transgenic birds and eggs thereof, wherein the eggs contains a post translationaly modified exogenous protein. The experimentation required would further include making di-cistronic vector, encoding any and all proteins and modifying enzymes. In addition, experimentation required would include identification of signal sequences that directs the deposition of transgene product onto the yolk of a transgenic egg.

Conclusion

No claims are allowed.

Claims 19, 21, 25, 27, 29, 33-35, 41-57 are free of prior art. The art at the time of filing does not teach or suggest the making of a transgenic bird wherein the exogenous gene is expressed in the tubular gland cells of its magnums and the protein is deposited in eggs, wherein the protein deposited into the egg are post translatioinally modified proteins.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned as (703) 308-2035. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

S. Kaushal, AU 1633

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600